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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/900,518	07/06/2001	Keith D. Allen	R-716	3954

26619 7590 07/13/2004

DELTAGEN, INC.
1031 Bing Street
San Carlos, CA 94070

EXAMINER	
QIAN, CELINE X	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 07/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/900,518	ALLEN ET AL.	
	Examiner	Art Unit	
	Celine X Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *29-36,38 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *29-36,38 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/6/01* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 29-36, 38 and 39 are pending in the application.

This Office Action is in response to the Amendment filed on 4/19/04.

Response to Amendment

The objection to claim 37 is moot in light of Applicant's cancellation of the claims.

The rejection of claims 36 and 37 under 35 U.S.C. 112 2nd paragraph has been withdrawn in light of Applicant's amendment of the claims.

Claims 29-36, 38 and 39 are rejected under 35 U.S.C. 101/112 1st paragraph for reasons given below.

New Grounds of Rejection

Claims 29-36, 38 and 39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are drawn to a transgenic mouse whose genome comprises a disruption in an endogenous CX2 gene, wherein the disruption is homozygous, the transgenic mouse lacks production of functional CX2 protein, and exhibits, relative to a wild type mouse, increased seizure susceptibility, increased glucose tolerance, increased ability to metabolize glucose, increased body weight, increased body length and increased body weight to body length ratio. The claims are further drawn to a cell or tissue isolated from said mouse, a CX2 targeting construct, a method of making said targeting construct and a method for producing said mouse.

No well-established utility exists for the claimed transgenic mouse and cells or tissues isolated from said mouse. However, the specification asserts or implies the following as

credible, specific and substantial patentable utilities for the claimed transgenic knockout mouse and cells or tissues isolated from said mouse:

1) To be used in methods of identifying agents capable of affecting a phenotype of said mouse.

2) To identify agents useful as therapeutic agents for treating conditions associated with a disruption or other mutation of the CX2 gene.

3) To identify agents modulate the effect or activity of CX2.

4) To serve as models for diseases.

5) To test and develop new treatments relating to the behavioral phenotypes.

The specification discloses that the homozygous CX2 knockout mouse exhibits, relative to a wild type mouse, increased seizure susceptibility, increased glucose tolerance, increased ability to metabolize glucose, increased body weight, increased body length and increased body weight to body length ratio. The prior art does not teach the genotypic-phenotypic association of disruption of CX2 receptor and the disclosed phenotype is correlated with any specific diseases. As such, the asserted utility for the claimed mouse to be a disease model or screening therapeutic agents for treating diseases is not credible. In addition, the specification does not teach any utility for the agents that affect this phenotype. Therefore, the asserted utility for using the claimed mouse to identify agents that affect this phenotype is not substantial since there is no substantial use for such agents.

In addition, the claimed phenotype of increased body weight, increased body length and increased body weight and body length ratio and increased susceptibility to seizure is not credible. Figure 3 display the differences of the body weight between wild type and

homozygous CX2 knockout mouse. According to this figure, the difference does not have statistical significance because all mouse seem to have a body weight between 35g to 40g, whereas the wild type seems to be slightly heavier. It is rather contradictory to the claimed phenotype of the knockout mouse which supposes to have increased body weight. The other phenotype of increased body length and increased body weight and body length ratio and increased susceptibility to seizure are not supported by any experimental data. As such, without further support, this asserted utility is considered not credible.

Since the claimed transgenic mouse and cells/tissues isolated from said mouse does not have utility, the targeting construct, the method of making said construct and a method of producing said transgenic mouse does not have utility either. Therefore, the claimed invention lacks patentable utility for reasons given above.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 29-36, 38 and 39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Furthermore, even if the claimed invention were shown to have utility, it would not be enabled for following reasons.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the Invention:

Claims 29-36, 38 and 39 are drawn a transgenic mouse comprising a disruption in the CX2 gene, wherein the disruption is homozygous, the transgenic mouse lacks production of functional CX2 protein, and exhibits, relative to a wild type mouse, increased seizure susceptibility, increased glucose tolerance, increased ability to metabolize glucose, increased body weight, increased body length and increased body weight to body length ratio. The claims are further drawn to a cell or tissue isolated from said mouse, a CX2 targeting construct, a method of making said targeting construct and a method for producing said mouse.

Breadth of claims and amount of guidance in the specification and working Examples:

In the instant case, the claims encompass both heterozygous and homozygous CX2 transgenic knockout mouse, wherein the disruption is homozygous, the transgenic mouse lacks production of functional CX2 protein, and exhibits, relative to a wild type mouse, increased seizure susceptibility, increased glucose tolerance, increased ability to metabolize glucose, increased body weight, increased body length and increased body weight to body length ratio.

The specification does not provide an enabling disclosure for how to use the transgenic mouse as claimed. The specification does not provide specific teaching on how to use the transgenic knockout mouse without a phenotype or with a transgene independent phenotype. Further, the specification fails to teach how to use the transgenic mouse with the disclosed phenotype of increased sensitivity to pain. The specification only prophetically teaches that the transgenic mouse can serve as models for diseases, screening drugs for treating the disease, screening agents that modulates a phenotype of said mouse, or screening agents that modulate the function or expression of the CX2. The specification fails to teach what type of diseases are associated with this disclosed genotypic vs. phenotypic correlation, or the phenotype of increased glucose tolerance, increased ability to metabolize glucose exhibited by the transgenic knockout mouse. In addition, as discussed in the 101 rejection, the phenotype of increased body weight, increased body length and increased body weight and body length ratio and increased susceptibility to seizure is not supported by the instant specification. As such, whether the CX2 transgenic knockout mouse can serve as any disease model or screening drugs to treat disease is unpredictable. Likewise, whether cells or tissues isolated from said mouse can be used for this purpose is unpredictable. The specification also fails to teach how to use an agent that modulates this phenotype associated with CX2 gene disruption. In addition, the specification fails to teach how to screen agents that modulate the effect and activity of the CX2 in a mouse (or cells or tissues isolated from said mouse) does not express said gene. As such, one skilled in the art would not know how to use the transgenic mouse without any phenotype (i.e. heterozygotes) or with the phenotype of increased sensitivity to pain for the above embodiments. Similarly, one skilled in the art would not know how to use the cells or tissues isolated from said mouse. As

such, the specification does not provide sufficient guidance for the enablement of the claimed mouse. Since the targeting construct is used for producing said mouse (which one does not know how to use), the targeting construct, the method of making said construct and the method of producing said mouse also lack enablement by the instant specification.

The state of art and the level of predictability in the art:

The prior art teaches that the phenotype of a transgenic or knockout animal is highly unpredictable. When considering the predictability of the phenotype of a transgenic mouse, one has to remember that the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied and the effect of allelic variation and the interaction between the allelic variants (pg.1425, paragraph 1 in Sigmund, C.D. 2000. Arterioscler Thromb Vasc Biol.20:1425-1429). Sigmund indicate that the genetic background is the collection of all genes present in an organism that influences a trait or traits. These genes may be part of the same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Such genetic background and "epigenetic" effects, such as allelic variants between different strains of mouse, can dramatically alter the observed phenotype. Moreover, the particular genetic elements required for expression varies from species to species. For example, Jacks et al. (1992) describe Rb KO mice that do not display retinoblastoma; rather they exhibit the unexpected phenotype of pituitary tumors. The pituitary tumors arise from cells lacking a wild-type Rb allele. Thus, tumors were found to arise not in retinas, as in humans, but in the pituitary gland (page 299, Discussion, paragraphs 1 and 3). As such, whether the disclosed phenotype of said knockout mouse can be used to predict CX2 function in human is unpredictable. As such, without teaching from the specification, one skilled

in the art would not know how to use the claimed mouse with the disclosed phenotype since such phenotype only exists in mouse. Therefore, whether the claimed mouse can be served as a disease model or screening drugs or treatments is unpredictable. Similarly, whether cells or tissues isolated from said mouse can be used for this purpose is also unpredictable.

Moreover, the claims encompass both heterozygotes and homozygotes. However, since heterozygotes have one functional allele, the heterozygotes would not be expected to have the same phenotype as the homozygotes. The specification does not teach whether the heterozygotes have the same phenotype as the homozygotes. As such, the phenotype of a heterozygotes is unpredictable, and the specification, in the instant case, is not enabling for a transgenic knockout mouse that exhibits no phenotype or that exhibits transgene-independent phenotypes.

The state of art at the time of filing considers generating null mutation of a specific gene in mice and phenotypic behavior resulted from the mutation as unpredictable. Crawley et al. (1997, Psychopharmacology, Vol 132, pages 107-124) teaches that the phenotype of a mutant mouse is not only the result of the targeted gene, but it also reflects interactions with background gene, and other unknown mutations in the genetic background (see pages 107 last paragraph through page 108 1st paragraph). The article further teaches that not all isogenic backgrounds are appropriate for a given study, since the behavioral characteristics of certain isogenic strains could overshadow the effects of the targeted mutations (see page 108, 1st col., lines 10-14). Moreover, two strains commonly used in ES cell and knockout generation C57BL/6 and various substrains of 129 are unusual on many standard behavioral paradigms. The unique traits of 129 and C57BL/6 mice are examples of a widespread problem for interpretation of behavioral phenotypes of null mutations, given the genetic diversity that exists amongst the dozens of other commonly

available inbred mouse strains (see page 108, 2nd paragraph). Therefore, whether the behavioral phenotype of increased susceptibility to seizure is result from null mutation alone is unpredictable. As such, whether the claimed mouse can be used to develop new treatments for behavioral phenotype is unpredictable.

The state of art at the time of the filing is silent on a transgenic mouse whose genome comprises a disruption in an endogenous CX2 gene, wherein the disruption is homozygous, said mouse exhibits phenotypic feature of increased seizure susceptibility, increased glucose tolerance, increased ability to metabolize glucose, increased body weight, increased body length and increased body weight to body length ratio, as compared to a wild type mouse. Without teaching from the specification, one skilled in the art would not know how to use the claimed transgenic mouse. Since the mouse is not enabled, the cell or tissue isolated from the mouse, the targeting construct, the method for making the construct and the method for producing said mouse are not enabled either. Without teaching from the art and lack of sufficient guidance from the specification, one skilled in the art would have to engage in undue experimentation to use the inventions as claimed. Therefore, the claimed inventions are not enabled by the instant specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 571-272-0777. The examiner can normally be reached on 9:30-6:00 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Celine Qian, Ph.D.